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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/848,820	05/19/2004	Timothy A. McKinsey	MYOG:044US	4787

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FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

EXAMINER	
PETERSEN, CLARK D	
ART UNIT	**PAPER NUMBER**
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/848,820	MCKINSEY ET AL.	
	Examiner	Art Unit	
	Clark D. Petersen	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 7 September 2007, in which claims 12-89 were canceled and claim 1 was amended.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

All objections and rejections not repeated in the instant Action have been withdrawn due to Applicant's response to the previous Action.

Drawings

Applicants' submittal of corrected drawings for Figs. 6A and 6B is acknowledged. Based on the replacement drawings, the objection in the Action mailed 7 March 2007 is withdrawn.

Response to arguments - 35 USC § 112

Applicants traverse the rejection of claims 1-18 and 100 under 35 USC 112, first paragraph, as lacking enablement. Applicants have cancelled claims 12-18. However regarding claims 1-11 and 100, Applicants argue that the rejection cannot be applied because the therapeutic agents in question, such as staurosporine and beta blockers, are well known and that the skill of those in the art is high enough to understand their use. Examiner has argued that Applicants have provided no working examples of treating patients with drugs that modulate PKD in the function of ameliorating cardiac

hypertrophy. However upon consideration of the MPEP (see specifically 2164.02), it is not required that Applicants provide detailed examples of *in vivo* protocols provided that the *in vitro* results are expected to correlate to *in vivo* results. Therefore the rejection of claims 1-11 and 100 as lacking enablement as a result of providing no working examples is withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 7, 9, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Dempsey (US 6,228,843, issued 8 May 2001) in light of Wang (Trends Pharmacol Sci, June 2006) and Matthews et al (J Biol Chem, August 1997).

This is a new rejection necessitated by Applicant's amendment.

Dempsey teaches a method of treating cardiac hypertrophy and cardiac failure. They teach that treatment can comprise administering several drugs to inactivate protein kinase C. Specifically the drugs they teach include bryostatin and Go6976 (see Fig. 4; see col. 3 line 62 to line 67, as examples). Wang teaches that PKD is phosphorylated by PKC. Dempsey teaches that his method functions by first activating PKC which then causes its degradation (see col. 11 lines 35-40, for example). Matthews et al teach that bryostatin activates PKD through PKC (see Abstract, for

example); therefore it is inherent that administration of bryostatin causes degradation of PKC and inhibition of PKD signaling as taught by Dempsey. These drugs are effective in primates including humans, reading on the limitation that the patient is human (see col. 4, lines 1-6, for example). Among the drugs administered can be staurosporine, for example (see col. 12, lines 32-45, for example). They teach that the drugs can be administered in an oral or intravenous manner (see col. 6 lines 39-53, for example).

Therefore the teachings of Dempsey are deemed to anticipate instant claims 1-4, 7, 9, and 10.

Response to arguments - 35 USC § 102

Applicants traverse the rejection of claims 1-6, 8-18 and 100 as being anticipated by Bucholz et al (Hypertension, 1991) in light of Bing et al (Heart Failure Rev, Jan 2002).

Based on Applicants' arguments and amendments to the claims, that rejection is withdrawn. However, as discussed below, Buchholz et al is maintained as rendering the instant claims unpatentable under 35 USC 103(a).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11 and 100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buchholz et al (Hypertension, 1991) in view of Bing et al (Heart Failure Rev, Jan 2002).

This rejection was previously presented under 35 USC 102(b) in the Office Action mailed 7 March 2007, and is slightly modified as necessitated by Applicants' amendment.

Buchholz et al teach a method of administering staurosporine to spontaneously hypertensive rats. Hypertension is known as a risk factor for hypertrophy, therefore selection of these rats reads on identifying a patient at risk of hypertrophy. Additionally spontaneously hypertrophic rats are well characterized as developing hypertrophy in response to their hypertensive disease (see Bing et al, 2002). They teach that one can administer staurosporine to rats intravenously and record arterial pressure and cardiovascular activity (see p. 93, col. 2, for example). They also administer staurosporine by gavage, reading on oral administration (see p. 93, col. 2, for example). They administer a second therapeutic, namely the beta blocker nadolol, to rats 5 min before intravenous administration of staurosporine. They teach that this combination lowers mean arterial pressure and decreases tachycardia (see Fig. 5, p. 97; see text, p. 95 last paragraph to p. 96, col. 1, as examples). The methods taught by Buchholz et al inherently have the results cited in claim 100. Regarding the limitation of claim 7 that administration of a beta blocker occurs simultaneously with staurosporine, it would be an obvious matter of convenience to the artisan whether to administer the drugs simultaneously or five min apart.

Bing et al teach that the spontaneously hypertensive rat is an ideal model for studying heart failure and hypertrophy as it applies to human disease (see Abstract, p. 71, col. 1, for example). They teach that that it is normal practice to measure heart failure and heart improvement through measurements of cardiac output such as ejection fraction (see Introduction, p. 71, col. 2 for example). Additionally they teach that it is possible to measure changes in ejection fraction in spontaneously hypertensive rats approaching heart failure; they also teach that mortality is a useful parameter for measuring cardiac response to drug treatment (see "Prevention and Treatment of Heart Failure", p. 76, for example).

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer a PKD inhibitor such as staurosporine, alone or in combination with a beta blocker, to a human patient suffering from or suspected of suffering from cardiac hypertrophy or cardiac failure.

Response to arguments - 35 USC § 103

Applicants amended the claims such that the teachings of Buchholz et al no longer apply under 35 USC 102(b). However, because Examiner has applied the teachings of Buchholz et al under 35 USC 103(a) in this Office Action, it is important to respond to Applicants' arguments regarding the Buchholz and Bing references.

Applicants argue several points. Applicants contend that the rats described by Buchholz et al do not match the criteria of the instant claims because they are spontaneously hypertensive. This condition only manifests itself at 2 months followed

by "a long period of stable hypertension and compensatory hypertrophy" (Buchholz et al, p. 72). The best evidence is that the rats in the Buchholz et al reference were studied at 15-17 weeks. As acknowledged, by Applicants, this period is well within the window after initiation of hypertension.

Cardiac hypertrophy is a result of chronic conditions such as hypertension. Two reviews are provided with the instant Office Action: see Wang (Current Opin Pharmacol, 2001) and Lorell et al (Circulation, 2000). For example Wang makes a distinction between phases of cardiac hypertrophy, but not between ultimate results of chronic hypertrophy. Wang teaches that all hypertrophy is compensatory, in that a thickening of the wall of the heart compensates for other pathological conditions such as hypertension. However sustained hypertrophy results in damage to the heart itself, regardless of reason (see Introduction, p. 134, col. 1, and first para col. 2, for example). Furthermore Lorell et al teach criteria for determining whether cardiac hypertrophy is deleterious or not. They teach that it is not deleterious in 3 settings: maturation in infancy and childhood, pregnancy, and exercise (see "Detection of Physiological Hypertrophy", p. 473, col. 1, for example). Lorell et al specifically mention hypertension as a factor in pathological hypertrophy (see p. 470, col. 2, for example). Therefore any sustained cardiac hypertrophy is pathological, and for this reason examiner does not agree with Applicants' assertion that the cited art is not applicable because it discusses a different type of cardiac hypertrophy.

There are two inherent factors at work in the literature cited. It should be acknowledged that the instant application was examined only for the method steps

claimed, not for the molecular biology underlying the method steps. Applicants claimed a method of administering staurosporine or beta blockers. Applicants have argued that it would not have been obvious to administer the combination, because one of ordinary skill in the art (i.e. Buchholz) was expecting to treat hypertension, not cardiac hypertrophy. However cardiac hypertrophy is a symptom of hypertension. One would have inherently been treating cardiac hypertrophy regardless of whether the intent was to directly address a factor leading to hypertrophy, not hypertrophy itself. The outcome is the same. Furthermore, it is acknowledged that no citation reciting method steps explicitly states that protein kinase D is the intended target of staurosporine treatment, for example. Protein kinase D is a signaling factor that lies downstream of PKC. Because the cited references treat PKC with staurosporine, they inherently treat PKD activity. Intended consequences cannot be considered when considering whether method steps of prior art anticipate or make obvious method steps as instantly claimed. Because the steps are the same, the outcome must be the same. Furthermore, the motivation need not be the motivation provided in the instant application, so long as there exists a motivation to use the same drugs in humans as in a rat population. Bing teaches that humans with hypertension can be treated analogously to rats with hypertension; several of the references teach that hypertension in humans leads to cardiac hypertrophy in humans. Therefore, motivation exists to treat humans with staurosporine and beta blockers, regardless of whether the practitioner knew he was treating protein kinase D or not.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Clark D. Petersen whose telephone number is (571)272-5358. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571)272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CDP
11/15/2007

Jon Weber
Supervisory Patent Examiner